PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Reports of myocarditis and pericarditis following mRNA COVID-19 vaccination: a systematic review of spontaneously reported data from the UK, Europe, and the US and of the scientific literature
AUTHORS	Lane, Samantha; Yeomans, Alison; Shakir, Saad

VERSION 1 – REVIEW

REVIEWER	Das, Bibhuti The University of Mississippi Medical Center, Pediatrics
REVIEW RETURNED	09-Jan-2022

GENERAL COMMENTS	This study summarized he incidence as reported to VAERS from UK, Europe and USA. It is updated until October 21, 2021. Since then, there have been numerous other case series and multicenter studies published to describe the variability in diagnosis, treatment in children and adults. 1. The data from UK appears to be more representative because of yellow card system. Authors should make a flow diagram to start with how many published reports they reviewed and how they the limited total studies (ref 29,30, and 31) they included in Table-5. Please describe their inclusion and exclusion criteria. There are many large series of cases from children in USA are missing. 2. Table-2 described the overall VAERS, then Table3a (Pfizer) and Table-3b (Moderna): the total of Table 3a and 3b are not adding up to Table-2. These indicate self reporting from centers to VAERS and those published in the case series are much higher than companies reported. Authors should describe why the low numbers reported by the both mRNA vaccine comapnies. is the case definition is different. CDC has defined the definition and authors should highlight the differences in UK and European region in defining mRNA VAM. 3. It is not clear to me all the source of patients that included in this study. 4. How the case definition of mRNA VAM in US differs in UK and Europe, and those defined per CDC and the companies reporting. 5. Any cases reported from other vaccine such as Janssen in UK and Europe. 6. The authors report are little delayed in all aspects: e.g. first case report from Israel in May (it is actually in April). 7. Any case fatality reported in adults vs children. 8. In authors view, speculation of any mechanism of VAM. Some cases are reported after 3 doses and 2 cases after 5 doses. Are these same as after 1 dose or after 2nd dose. 9. It is useful to know if there is any geographical difference in UK, Europe from US. Myocarditis due to viral etiology is different across Atlantic. Although same mRNA vaccine is used all over,

	there is always a difference bases on host/genetic response especially innate immunity.

REVIEWER	Oudit, Gavin University of Alberta
REVIEW RETURNED	01-Mar-2022

GENERAL COMMENTS	In this study, Lane et al. analyzed the UK, US and EU public spontaneous reporting databases to examine the incidence of myocarditis and pericarditis following COVID-19 mRNA vaccination. In total, 5295 reports of myocarditis, and 3453 reports of pericarditis were identified during the study period. Authors also conducted a systematic review of published observational studies (case reports or case series were excluded). The main findings were that individuals with adverse events of myocarditis/pericarditis were more likely males, <40 years of age, and frequently occurred after the second dose. Additionally, the cases are mostly mild and resulted in full recovery. Overall, the manuscript reaffirms many findings on this topic that are already available in the literature. I have a few specific comments below. 1. Authors stated more incidence of adverse events were reported after Pfizer/BioNTech vaccination (73.3%). This statement may not be accurate considering that a lot more individuals included in this study happened to also receive the Pfizer vaccine. Indeed, analyses adjusting for differences in sex, age, doses, and vaccine type were not conducted in the current study but presented as descriptives only. 2. Could the authors please expand on the potential sources of heterogeneity between studies of vaccine induced myocarditis/pericarditis included in the systemic review and the steps taken to account for these in the analysis? 3. There was an issue with the display of figure 1 in the proof, where the histograms were not clearly present. In addition, a flow chart of search strategy and filtered studies for the systematic review would be appropriate. 4. Authors should consider including the diagnostic criteria for myocarditis or pericarditis in the respective studies in Table 5. 5. The risk ratio from each study included in the systemic review should be presented as a figure. 6. In the discussion, authors stated the possibility of an underreporting of events to regulators may result in a lowered prevalence of actual myocarditis/pericarditis event but should also consider the possibility that an over-estimation may stem from various factors such as COVID-19 waves during the study period, and cases unrelated to the mRNA vaccination that would require more in-depth clinical evaluation. 7. The difference in vaccine roll-out should be considered for the differences between regions, in addition to younger individuals were more likely to receive mRNA vaccines as mentioned, some studies have also reported the time lag between 2 doses may play a role in myocarditis/pericarditis rates following vaccination. 8. The authors can update some of the references cited in the manuscript with more recent publications including key epidemiological studies for mRNA vaccine induced myocarditis/pericarditis published over the past few months. As it stands, many references are press release, news reports and society recommendations.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Bibhuti Das, The University of Mississippi Medical Center Comments to the Author:
This study summarized he incidence as reported to VAERS from UK, Europe and USA. It is updated until October 21, 2021. Since then, there have been numerous other case series
and multicenter studies published to describe the variability in diagnosis, treatment in children and adults.

1. The data from UK appears to be more representative because of yellow card system. Athors should make a flow diagram to start with how many published reports they reviewed and how they the limited total studies (ref 29,30, and 31) they included in Table-5. Please describe their inclusion and exclusion criteria. There are many large series of cases from children in USA are missing.
Thank you for your advice, we have completed an updated the systematic literature review to produce the most up-to-date review as possible as well as carried this out by two independent researchers. We have included a flowchart of the systematic literature search in figure 1 as well as updated our results section, page 5, lines 148-153. The inclusion and exclusion criteria are detailed in our materials and methods section, page 5, line 126-141. We have excluded case series (page 5, line 127) from our analysis to provide a comprehensive analysis of the population as a whole rather than focusing on discrete subgroups in this analysis.

2. Table-2 described the overall VAERS, then Table3a (Pfizer) and Table-3b (Moderna): the total of Table 3a and 3b are not adding up to Table-2. These indicate self reporting from centers to VAERS and those published in the case series are much higher than companies reported. Authors should describe why the low numbers reported by the both mRNA vaccine comapnies. is the case definition is different. CDC has defined the definition and authors should highlight the differences in UK and European region in defining mRNA VAM.
We thank you for pointing this out, in order to address other comments we received we have completely updated these tables with as up to date as possible data. We have also included in the limitations of this study in a sentence regarding this issue of differing definitions used, please see page 10, line 367. We have not directly compared our data with data recorded by mRNA companies as we have analysed spontaneous reporting of events from healthcare professionals and consumers (page 4, lines 106-107), although we would like to draw your attention that both our analysis and data released from marketing authorisation holders agree that this is a very rare event in response to the vaccine.

3. It is not clear to me all the source of patients that included in this study.
We apologise that this was not clear and we hope that the new version will provide greater clarity to the induced sources of information. We have updated the materials and methods to provide an explanation of the where the data is received by the spontaneous reporting systems (Page 4, lines 102-112). We hope that the inclusion of the PRISMA flow chart (figure 1) and tables 5 and
6 provide greater detail on the included studies.

We have re-structured the results section such that each finding has its own sub-heading and includes all the information split into data from the UK Yellow card system, followed by data from the US VAERS system, the EU EudraVigilance system and last (but not least) the data retrieved from the literature that also contributes to each finding. The results section starts on page 5, line 146.

4. How the case definition of mRNA VAM in US differs in UK and Europe, and those defined per CDC and the companies reporting.

Unfortunately due to the nature of spontaneous reporting systems we are not able to specify the definitions used, only that all reports had be coded as myocarditis or pericarditis. We have added a sentence into the limitations to address this, page 10, line 367-370.

5. Any cases reported from other vaccine such as Janssen in UK and Europe.
This is a very insightful suggestion but is beyond the scope of this manuscript, detailed analysis of myocarditis and pericarditis following other COVID-19 vaccines would require a similar investigation to the one that we have described here.

6. The authors report are little delayed in all aspects: e.g. first case report from Israel in May (it is actually in April).
We apologise for this difference in the dates, but we are unable to find the publication dated April for the study from Israel. We appreciate that the publication dated in May will include cases between December 2020 and May 2021, to avoid any confusion we have removed reference to May 2021 (page 7, line 212).

7. Any case fatality reported in adults vs children.
We have addressed this in the new results subheading 3.3 (page 6-7, lines 192-206), for events where data was available on ages of fatal cases.

8. In authors view, speculation of any mechanism of VAM. Some cases are reported after 3 doses and 2 cases after 5 doses. Are these same as after 1 dose or after 2nd dose.
Thank you for this interesting question, unfortunately mechanism of action could only be speculated once causality has been confirmed; we would not like to propose a mechanism of action without greater evidence of causality. We believe that the data we describe here will enhance the understanding of these conditions and help with identification of potential sources of mechanisms by identifying which populations are most likely to suffer the adverse event of myocarditis and pericarditis following COVID-19 mRNA vaccination. We have added this into the conclusion of our paper on page 11, lines 421-424.

9. It is useful to know if there is any geographical difference in UK, Europe from US. Myocarditis due to viral etiology is different across Atlantic. Although same mRNA vaccine is used all over, there is always a difference bases on host/genetic response especially innate immunity.
This is a very interesting area of virology and immunology that would require greater analysis. While a detailed specific answer is beyond the scope of our study, we have included data from the start of vaccine launch until 16th March 2022 and during this time interval of 15 months there have been multiple strains of COVID-19 circulating in all regions, as well as regional viruses. The data we described demonstrates that the trends identified, younger males being most susceptible to these adverse events, are maintained across different regions, verified through the spontaneous reporting systems as well as the literature. We have addressed this point in the discussion on page 9, lines 305-314.

Reviewer: 2
Dr. Gavin Oudit, University of Alberta
Comments to the Author:
In this study, Lane et al. analyzed the UK, US and EU public spontaneous reporting databases to examine the incidence of myocarditis and pericarditis following COVID-19 mRNA vaccination. In total, 5295 reports of myocarditis, and 3453 reports of pericarditis were identified during the study period. Authors also conducted a systematic review of published observational studies (case reports or case series were excluded). The main findings were that individuals with adverse events of myocarditis/pericarditis were more likely males, <40 years of age, and frequently occurred after the

second dose. Additionally, the cases are mostly mild and resulted in full recovery. Overall, the manuscript reaffirms many findings on this topic that are already available in the literature. I have a few specific comments below.

1. Authors stated more incidence of adverse events were reported after Pfizer/BioNTech vaccination (73.3%). This statement may not be accurate considering that a lot more individuals included in this study happened to also receive the Pfizer vaccine. Indeed, analyses adjusting for differences in sex, age, doses, and vaccine type were not conducted in the current study but presented as descriptives only.
We thank the reviewer for making us aware of this and have removed this sentence from the abstract. We have updated our data with the most up to date available and calculated reporting rates per million vaccine doses for each region within the results section to account for these variabilities. We have additionally re-structured the whole results section (starting on page 5) to investigate the effect of age, sex and dose of reports of myocarditis and pericarditis. Unfortunately, due to the nature of the data available we cannot adjust for these characteristics in our analysis.

2. Could the authors please expand on the potential sources of heterogeneity between studies of vaccine induced myocarditis/pericarditis included in the systemic review and the steps taken to account for these in the analysis?
We thank the reviewer for this comment but due to the limited number of publications at this stage since initiation of vaccination meant we could not limit according to study design where data would have been more comparable. In future, once further research has been conducted, it would be appropriate to conduct a meta-analysis to determine risk factors for myocarditis and pericarditis following COVID-19 mRNA vaccination. In order to address this issue we have amended the sentence on page 11, lines 388-390.

3. There was an issue with the display of figure 1 in the proof, where the histograms were not clearly present. In addition, a flow chart of search strategy and filtered studies for the systematic review would be appropriate.
We apologise for this issue. We have updated our data to address other comments we have received; therefore all figures and tables have been updated and we hope all formatting issues have been resolved.

4. Authors should consider including the diagnostic criteria for myocarditis or pericarditis in the respective studies in Table 5.
In order to provide a comprehensive overview of the literature data we have included observational studies of differing designs, some have included medical health care records that would only describe cases as those with the terms “myocarditis” or “pericarditis”, therefore diagnostic criteria was not always available, so we do not feel this would be appropriate to tabulate.

5. The risk ratio from each study included in the systemic review should be presented as a figure.
This would be an ideal visualisation of all published data, although due to differing study designs included not all studies provided a risk ratio; where these have been stated we have tabulated in Table 5. In order for this literature data to contribute to the main conclusions of the paper we have sub-divided the results section into focused areas with the literature evidence contributing to each finding alongside the spontaneous reporting data.

6. In the discussion, authors stated the possibility of an underreporting of events to regulators may result in a lowered prevalence of actual myocarditis/pericarditis event but should also consider the possibility that an over-estimation may stem from various factors such as COVID-19 waves during the

study period, and cases unrelated to the mRNA vaccination that would require more in-depth clinical evaluation.
We thank the reviewer for this comment and have added a sentence in the discussion, page 9, lines 305-314. We agree that some of the spontaneous reports of myocarditis and pericarditis could have been caused by COVID-19 infection or other factors. However, it is not possible to identify or quantify these reports (page 9, lines 306-308).

7. The difference in vaccine roll-out should be considered for the differences between regions, in addition to younger individuals were more likely to receive mRNA vaccines as mentioned, some studies have also reported the time lag between 2 doses may play a role in myocarditis/pericarditis rates following vaccination.
This is a very interesting point, the roll-out of vaccines was different in the regions with corresponding differences in the age of profiles of people in the different regions. For example, the most widely used vaccine in the UK during the first quarter of 2021 was the AstraZeneca DNA COVID-19 vaccine which is not authorised in the US, and we have added a sentence into the discussion on page 9, lines 301-303. However, regarding mRNA vaccines, even though there may have been different time delays in receiving the second vaccine between regions (and indeed in the UK this was altered due to COVID-19 infection waves), of all the data we analysed the majority of events were reported following the second dose.

8. The authors can update some of the references cited in the manuscript with more recent publications including key epidemiological studies for mRNA vaccine induced myocarditis/pericarditis published over the past few months. As it stands, many references are press release, news reports and society recommendations.
We have updated our systematic literature review to incorporate the most recent findings, which has been updated in the results section and throughout.

VERSION 2 – REVIEW

REVIEWER	Das, Bibhuti The University of Mississippi Medical Center, Pediatrics
REVIEW RETURNED	16-Apr-2022

GENERAL COMMENTS	The authors adequately addressed all my queries.